

## Appendix II

J Am Soc Nephrol 12: 2001

Clinical Nephrology: Chronic Renal Disease

A0451

SUI-0500 (PS)

**Renoprotective Effects of 2-Hydroxyestradiol.** Stevan P. Tofovic,<sup>1,2</sup> Raghvendra K. Dubey,<sup>1,3</sup> Sheldon I. Bastacky,<sup>4</sup> Edwin K. Jackson.<sup>1,3</sup> <sup>1</sup>Center for Clinical Pharmacology; <sup>2</sup>Departments of Medicine; <sup>3</sup>Pharmacology; <sup>4</sup>Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA; <sup>5</sup>Department of Obstetrics and Gynecology, Clinic for Endocrinology, University Hospital, Zurich, Switzerland.

Our previous studies demonstrate that 2-hydroxyestradiol (2-OHE), a metabolite of estradiol with little affinity for estrogen receptors, has greater antimitogenic effects on smooth muscle cells and fibroblasts compared with estradiol. In the present study we investigated the potential renoprotective effects of 2-OHE, both *in vitro* and *in vivo*. *In vitro* studies were conducted in isolated rat glomerular mesangial cells. 2-OHE concentration-dependently (0.001-1  $\mu$ mol/L) inhibited serum (2.5%)-induced cell growth as assessed by DNA synthesis (<sup>3</sup>H-thymidine incorporation). Importantly, the inhibitory effects of 2-OHE were not blocked by ICI182780 (100  $\mu$ mol/L), an estrogen receptor antagonist. Furthermore, 2-OHE inhibited serum-induced collagen synthesis (<sup>3</sup>H-proline incorporation) and cell proliferation. *In vivo* studies were conducted in male, obese (fa-fa<sup>fr</sup>) ZSF1 rats, a model of nephropathy associated with hypertension and the metabolic syndrome. 2-OHE (10  $\mu$ g/h/kg *via* osmotic minipumps) was given for 24 weeks. Chronic treatment with 2-OHE significantly reduced proteinuria (12 weeks: 369 $\pm$ 44 vs 185 $\pm$ 27 mg/day; 24 weeks: 586 $\pm$ 41 vs 333 $\pm$ 21 mg/day, control vs. 2-OHE, respectively;  $p$ <0.001) and the severity of glomerulosclerosis (11.1 $\pm$ 0.9 vs 6.7 $\pm$ 0.6%) and attenuated interstitial inflammation ( $p$ <0.05). This study indicates that 2-OHE exerts renoprotective effects that are mediated by estrogen receptor-independent mechanisms. The renoprotective effects of 2-OHE are due, at least in part, to inhibition of key proliferative mechanisms involved in glomerular remodeling and sclerosis.

Codes: FC – Free Communication; PS – Poster Session.

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